1. AMENDMENTS

1.1 AMENDMENTS TO THE SPECIFICATION:

Please amend the following paragraphs of the Specification as shown.

[0037] ~~FIG. 5 is a graph~~FIG. 5A, FIG. 5B, and FIG. 5C are graphs showing the results from size exclusion HPLC of immunoreactive NT-CNP (filled circles) and CNP-22 (open circles) in extracts of (FIG. 5A) EDTA plasma from normal adult human subjects, (FIG. 5B) pooled EDTA plasma obtained from children, and (FIG. 5C) EDTA plasma from sheep. Column void volume and the elution position of molecular weight markers are shown by arrows;

[0038] FIG. 6A and FIG. 6B show[[s]] the results from size exclusion HPLC of (FIG. 6A) pooled maternal plasma and (FIG. 6B) matching pooled cord plasma. Column void volume and elution positions or molecular weight markers are shown by arrows. Immunoreactive NT-CNP (closed circles) and CNP (open circles);

[0041] FIG. 9A, FIG. 9B, FIG. 9C and FIG.9D: Top panels; correlations between plasma NT-CNP in children (aged 5-18 years) and (FIG. 9A) plasma alkaline phosphatase activity, (FIG. 9B) height velocity. Bottom panels; correlations between plasma NT-CNP in growing lambs and (FIG. 9C) plasma alkaline phosphatase activity, (FIG. 9D) metacarpal growth velocity;

[0043] FIG. 11A and FIG. 11B: Effect of 4 days of treatment with a glucocorticoid (dexamethasone, 0.25 mg/kg/day) in 12 week old lambs (filled circles, n=8) and in adult sheep (open circles, n=8) on (A) plasma NT-CNP and (B) change (?) in plasma alkaline phosphatase activity (ALP). Values are mean ± SEM;

[0044] FIG. 12A, FIG. 12B, FIG. 12C and FIG. 12D: Effect of a glucocorticoid (dexamethasone, 0.25 mg/kg/day) (filled circles, n=8) or saline control treatment (open circles, n=8), administered

to 4 week old lambs for 15 days, on (FIG. 12A) plasma NT-CNP (FIG. 12B) plasma alkaline phosphatase activity (FIG. 12C) metacarpal length and (FIG. 12D) body weight. Values are mean ± SEM; and

[0085] In a currently more preferred embodiment, at least 15 consecutive amino acids from proCNP(1-81) is employed. For the best ability to raise antibodies, proCNP(1-81) can be employed itself. Other examples of peptides that could be used in raising antibodies include proCNP(1-50), proCNP(1-81), and proCNP(51-81) as set forth in ~~FIGS.~~FIG. 1 and FIG. 2. proCNP(1-103) can also be used in certain circumstances as antibodies raised may cross-react with proCNP(1-81) and proCNP(1-50) peptides. The peptides useful in the present invention are collectively referred to as NT-CNP in this application. The present invention also includes the use of functionally equivalent variants of the NT-CNP peptides.

[0096] Immunoassays specific for NT-CNP peptides require the production of antibodies that specifically bind to NT-CNP peptides. One such preferred antibody ~~recognises~~recognizes amino acids within proCNP(1-15). These antibodies, while being specific for NT-CNP peptides have broad NT-CNP specificity. Antibodies useful in the invention preferably bind to one or more of the four peptides proCNP(1-50), proCNP(1-81), proCNP(51-81) and proCNP(1-103) (~~FIGS.~~FIG. 1 and FIG. 2) or their metabolites. The antibodies can be used to construct immunoassays with broad specificity, as in competitive binding assays below, or used in conjunction with other antibodies described below in sandwich type assays to produce assays specific to each of the three peptides or to other NT-CNP peptides. Art-skilled workers will appreciate that non-competitive assays are also possible. The latter antibodies for sandwich immunoassays include those specific for amino acid sequences within proCNP(1-15), proCNP(36-50) and proCNP(67-81). These are preferred antibodies for use herein.

[0136] Human and ovine plasma contain NT-CNP: Plasma obtained from human umbilical cords, normal adults, children and sheep was extracted on Sep Pak columns and subjected to size exclusion HPLC (SE-HPLC) (~~FIGS. 5 and 6~~FIG. 5A, FIG. 5B, FIG. 5C, FIG. 6A and FIG. 6B). SE-HPLC showed the major immunoreactive NT-CNP peak in all these samples had a molecular

weight close to 5 kDa (fractions 29-30, ~~FIGS. 5 and 6~~FIG. 5A, FIG. 5B FIG. 5C, FIG. 6A and FIG. 6B). No immunoreactivity to antisera raised against CNP-22 could be demonstrated in these HPLC fractions.

[0140] As shown in ~~FIGS.~~FIG. 9A and FIG. 9B, there was a significant positive association in the 5-18 year age group between a marker of bone formation (ALP) and plasma NT-CNP ($r=0.55$, $p<0.001$), and height velocity with plasma NT-CNP ($r=0.57$, $p=0.005$).

[0145] Acute administration of the glucocorticoid dexamethasone, significantly reduces the blood level of NT-CNP, as well as alkaline phosphatase (a marker of mature chondrocyte population), in growing lambs (FIG. 11A and FIG. 11B).

[0146] As shown in FIG. 11A and FIG. 11B, dexamethasone 0.25 mg/kg/day for 4 days markedly reduced plasma NT-CNP and ALP in lambs but less so in adult sheep. This differential response to dexamethasone was highly significant for both NT-CNP ($F=5.4$, $p<0.001$) and ALP ($F=4.1$, $p=0.002$). After 48 hours of dexamethasone treatment, plasma NT-CNP in lambs fell $30.8 \pm 3.5\%$ from basal compared with $17.7 \pm 2.7\%$ in adult sheep. Both the onset and offset of dexamethasone's action on NT-CNP preceded that of ALP (FIG. 11A and FIG. 11B). Taken together these results are consistent with the greater volume of growth plate cartilage in growing lambs, compared with adult sheep.

[0147] In order to study a possible linkage between changes in NT-CNP and growth velocity, a more prolonged study was undertaken in younger growing lambs. As shown in FIG. 12A, FIG. 12B, FIG. 12C and FIG.12D, dexamethasone 0.25 mg/kg/day for 15 days in 4 week old lambs was associated with a highly significant fall in NT-CNP within 24 hours of starting treatment ($F=7.5$, $p<0.001$) and was sustained throughout the period of dexamethasone treatment and returned to control levels within 24 hours of cessation of treatment. Whereas plasma ALP activity also decreased during the treatment period ($F=1.9$, $p=0.029$, FIG. 12B) the onset and offset of response in ALP to dexamethasone was delayed when compared with that of NT-CNP.

Dexamethasone treatment was associated with a pronounced decrease in metacarpal elongation ($F=7.0$, $p<0.001$, FIG. 12C) which abated after restoration of NT-CNP levels.